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November 16, 2011

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ABSTRACT

Symptom Clusters and Work Limitations in Employed Breast Cancer Survivors

Michal Moskowitz, Master of Science, 2012

Thesis directed by: Michael Feuerstein, PhD, MPH, Professor, Medical and Clinical Psychology

Background: Symptoms can impair work outcomes in cancer survivors. There is research that symptoms occur in clusters in cancer patients; however, symptom clusters and work productivity have not been studied in cancer survivors years after cancer treatment. This study identified symptom clusters in employed breast cancer survivors (BCS) and explored whether clusters were related to work limitations. **Methods:** Hierarchical cluster analysis grouped BCS and a comparison sample using levels of fatigue, cognitive limitations, anxiety, and depressive symptoms. The groups were compared with work limitations as the dependent variable using one-way ANOVA. **Results**: A two cluster solution appeared in the BCS and comparison groups. In each sample, one cluster had higher levels of symptoms and greater work limitations compared to the other cluster. **Conclusion:** BCS, as well as a comparison group, report symptoms that cluster at two levels of severity. Those with high severity symptoms report lower work output.

SYMPTOM CLUSTERS AND WORK LIMITATIONS

IN EMPLOYED BREAST CANCER SURVIVORS

by Michal Moskowitz

Thesis submitted to the Faculty of the
Medical and Clinical Psychology Graduate Program
Uniformed Services University of the Health Sciences
in partial fulfillment of the requirements for the degree of
Master of Science 2012

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BACKGROUND

Work and cancer

Currently there are approximately 12 million cancer survivors in the U.S.("SEER Cancer Statistics Review, 1975-2006," 2009) With approximately 40% of cancer survivors in the U.S. of working age ("SEER Cancer Statistics Review, 1975-2006," 2009), the transition back to paid employment and ability to remain at work following diagnosis and treatment is a major concern for many cancer survivors. Studies have consistently found that among American, Canadian, and British cancer survivors who were employed at diagnosis, between 80-85% of survivors are employed between 18 months and 4 years after diagnosis (Amir, Moran, Walsh, Iddenden, & Luker, 2007; Bouknight, Bradley, & Luo, 2006; Drolet, et al., 2005; Short, Vasey, & Tunceli, 2005). Paid employment is important to cancer survivors for a number of reasons: Cancer survivors report that working is a sign of returning to normal life and it serves as an opportunity to be productive and creative (Johnsson, Fornander, Rutzvist, & Olsson, 2010). Cancer survivors also report that paid work provides needed income, provides access to health insurance (in the United States), serves as a distraction from the illness, and provides the survivor with a sense of self-worth and achievement (Main, Nowels, Cavender, Etschmaier, & Steiner, 2005).

Work loss following diagnosis is expected. In a sample of Canadian breast cancer survivors, the mean work absence length following cancer diagnosis was 7.5 months (Lauzier, et al., 2008). Because of work absence, workers lost 27% of their projected usual annual salary, representing a significant loss for cancer survivors, their families, and the economy at large. Also, once at work, cancer survivors in the United States are more likely to file disputes related to job loss and differential treatment related to workplace policies, compared with workers with other medical conditions (Feuerstein, Luff, Harrington, & Olsen, 2007), indicating a certain level of friction between empoyees and their employers.

Among the majority of cancer survivors who do return to work, many reduce their work because of cancer. In one community-based study of an American population of 100 heterogeneous survivors two years after diagnosis, 57% of cancer survivors who were working reduced work by more than 4 hours/week, with a mean reduction of 15 hours/week (Steiner, et al., 2008). Of these survivors, 81% reported that the reduction was due to cancer.

Late effects of cancer and their relationship with work ability

Late or long term effects of cancer and its treatment are common among cancer survivors. Fatigue is the most widely reported and often highly distressing symptom, affecting between one-quarter and one-third of breast cancer survivors up to 10 years after completion of treatment (Bower, 2008). Other common late effects include sleep disturbance, feelings of anxiety and depression, cognitive limitations, pain, and sexual dysfunction (Harrington, Hansen, Moskowitz, Todd, & Feuerstein, 2010; Shi, et al., 2011). These symptoms have been related to work limitations in many types of workers with and without chronic illness. These late and long-term effects appear related to cancer survivors' own perceptions of their work ability as well as tangible outcomes such as work retention. In one study of 100 American heterogeneous cancer survivors, reducing work hours was associated with experiencing more physical symptoms including lack of energy and more psychological symptoms including feeling anxious or depressed, although the direction of this relationship is unknown (Steiner, et al., 2008). Fatigue and cognitive functioning are also among the factors that impact on the cancer survivor's self-perceived work ability and are related to time to return to work after the first day of sick leave (de Boer, et al., 2008).

Studies of Northern European cancer survivors 2-6 years post-primary treatment have found that working cancer survivors reported lower physical and mental work capacity compared to a non-cancer control group (Gudbergsson, Fossa, Borgeraas, & Dahl, 2006; Gudbergsson, Fossa, & Dahl, 2008). These studies also showed that cancer survivors who made work changes due to cancer (e.g. changes in employer, occupation, work tasks, unemployment, or pensioning) reported lower perceived work ability, more anxiety and depression, and poorer physical and mental quality of life compared to cancer survivors who did not make work changes due to cancer (Gudbergsson, et al., 2008). Self-perceived work ability in cancer survivors, measured by comparing current work ability to lifetime best, is lower in those with neuropsychological impairment (as measured by performance below 1.5 standard deviations on more than one test of memory, concentration, attention executive function, psychomotor speed, auditory information procesing, and/or verbal fluency) compared to those without such impairment (Nieuwenhuijsen, de Boer, Spelten, Sprangers, & Verbeek, 2009).

A study of working breast cancer survivors an average of 4 years post-diagnosis found that breast cancer survivors experience higher levels of work limitations compared to a non-cancer comparison group (Hansen, Feuerstein, Calvio, & Olsen, 2008). In addition, in breast cancer survivors an average of 3-4 years post-diagnosis, work limitations are more strongly related to fatigue (Calvio, Peugeot, Bruns, Todd, & Feuerstein, 2010; Hansen, et al., 2008) and job stress (Calvio, et al., 2010) in breast cancer survivors than in a non-cancer comparison group.

Symptom clusters in cancer

Traditionally, the majority of research on symptom burden in cancer has studied particular symptoms such as fatigue or pain independently of one another (Dodd, Miaskowski, & Paul, 2001). Symptoms in cancer patients and survivors rarely occur in isolation, yet symptoms have been traditionally assessed and treated as separate entities rather than as collective aspects of a “common syndrome” (Cleeland, et al., 2003). The growing recognition of the importance of patterns of symptoms in impairing the function and well-being of cancer patients and survivors has led to the development of multiple symptom inventories in order to better assess and treat symptom burden in those diagnosed with cancer (Cleeland, et al., 2003).

In the last decade, an emerging body of research has turned attention to the study of symptom clusters (Barsevick, 2007; Barsevick, Whitmer, Nail, Beck, & Dudley, 2006; Bender, Ergun, Rosenzweig, Cohen, & Sereika, 2005; Chen & Lin, 2007; Dodd, Cho, Cooper, &

Miaskowski, 2010; Fan, Filipczak, & Chow, 2007; H. Kim, Barsevick, Tulman, & McDermott, 2008; Miaskowski & Aouizerat, 2007; Molassiotis, Wengstrom, & Kearney, 2010; Ridner, 2005; Thornton, Andersen, & Blakely, 2010; Xiao, 2010). Much of the symptom cluster literature uses the definition formulated by Dodd and colleagues, who stated that a symptom cluster consists of three or more concurrent symptoms that are related to each other, and may or may not share the same etiology (Dodd, Janson, et al., 2001).

Studies on symptom clusters to date have mostly used heterogeneous study populations of patients diagnosed with various types of cancer (Chen & Lin, 2007; Dodd, Miaskowski, et al., 2001; E. Kim, et al., 2009; Molassiotis, et al., 2010). Although breast cancer has been the cancer type most commonly studied for symptom clusters (Bender, et al., 2005; Dodd, et al., 2010; H. Kim, et al., 2008; Ridner, 2005), researchers have also identified symptom clusters in patients with lung cancer (Fox & Lyon, 2006) and gliomas (Fox, Lyon, & Farace, 2007). Across studies of breast cancer patients, similar symptom clusters have emerged: researchers have identified clusters of fatigue, cognitive impairment, and mood disturbance (Bender, et al., 2005); fatigue, cognitive impairment, depressed mood, insomnia, and pain (H. Kim, et al., 2008); fatigue, depressed mood, and pain (Thornton, et al., 2010); and fatigue, pain, depression, and insomnia (Dodd, et al., 2010).

Studying symptom clusters rather than studying individual symptoms may have implications for improving understanding mechanisms of symptoms. First, there is evidence that several symptoms, such as pain, fatigue, and depression, share common biomarkers (e.g. levels of corticosteroids and pro-inflammatory cytokines) which may indicate shared biological mechanisms (Miaskowski & Aouizerat, 2007; Thornton, et al., 2010). The understanding that symptoms in cancer patients may share a common underlying biological mechanism draws substantially from research on inflammatory cytokine-mediated "sickness behavior." Administration of cytokines such as interleukin-1 produces side-effects mediated by the central nervous system (Kelley, et al., 2003). These side effects are similar to the non-specific symptoms of sickness, such as malaise, fatigue, sleepiness, anorexia, apathy, difficulty concentrating, social withdrawal, and irritability. This constellation of symptoms has been called "sickness behavior" (Dantzer & Kelley, 2007; Kelley, et al., 2003). Sickness behavior is a term that describes both physiological and behavioral responses which have been studied primarily in animal models (Cleeland, et al., 2003). However there is also some evidence in human subjects that administration of cytokine therapy in non-cancer patients produces symptoms that resemble sickness behavior, e.g. fatigue, cognitive impairment, pain, and depressed mood (Cleeland, et al., 2003). Better research on the associations between symptoms is important for furthering the understanding of any biological mechanism underlying symptoms (Cleeland, et al., 2003).

Studying symptom clusters may also aid development of more effective assessment and innovative treatment of long-term and late effects. By identifying how symptoms cluster together in predictable patterns within individuals, and which patterns are associated with poorer functional outcomes (e.g. work), clinicians may be better positioned to identify individuals who are most likely to benefit from intervention targeted at reducing specific clusters of symptoms and ultimately improving functional outcomes. To the limited extent that previous studies have related symptom clusters with outcomes, they have examined the relationship between symptom clusters and quality of life (Dodd, et al., 2010; Fox & Lyon, 2006; Fox, et al., 2007) and physical performance status (Dodd, et al., 2010; Dodd, Miaskowski, et al., 2001), finding that greater symptom burden is associated with poorer quality of life and reduced physical function.

Understanding patterns of multiple symptom elevation rather than assessing individual symptoms is especially important when particular symptoms do not reach clinical levels. Subclinical levels of symptoms such as depression are common in cancer survivors; in these cases, the symptom level may not reach threshold for clinical diagnosis, but the symptom may cause distress as part of a wider symptom burden experience (Bower, 2008).

Ways of identifying clusters

Most studies of symptom clusters have used factor analysis or cluster analysis to group together symptoms that frequently co-occur rather than individuals who display similar patterns of symptoms (Dodd, et al., 2010). Although grouping individuals based on their pattern of symptoms is a less common approach, it has been used in a small number of studies (Dodd, et al., 2010; Miaskowski, et al., 2006; Shi, et al., 2011; Trask & Griffith, 2004). Using a large sample of 4,512 heterogeneous cancer survivors one year after diagnosis, generated from cancer registries in 11 states, Shi and colleagues (2011) performed a cluster analysis to differentiate between groups with high and low symptom burden. The high symptom burden group constituted 31% of the study sample and reported higher levels of a range of symptoms including fatigue, sleep disturbance, pain, low sexual interest, depressive symptoms, anxious feelings, and several gastrointestinal symptoms. The differences in symptom level between the high symptom and low symptom group were all medium-to-large effect sizes. The study found that fatigue, pain, and depression had the greatest impact on health-related quality of life (Shi, et al., 2011).

Trask & Griffith (2004) assessed 351 patients at a melanoma clinic at baseline and administered follow-up assessments at 2 months, 5 months, and 9 months. They identified four groups: 24% of the sample was "psychologically unhealthy" (reported high physical functioning and low pain, but high anxiety, nervousnes, and depression, and low problem-solving coping); 16% of the sample was "physically unhealthy" (reported poor physical functioning, severe pain and fatigue, and low anxiety); 7% of the sample was both psychologically and physically unhealthy, and 53% of the sample was healthy. The comparative level of distress and physical functioning in the groups remained fairly stable over the follow-up period, indicating that a subset of cancer survivors continues to experience a higher level of symptom burden even as more time elapses after completion of treatment (Trask & Griffith, 2004).

Miaskowski and colleagues (2006) assessed fatigue, sleep disturbance, pain, and depression in a sample of 191 heterogeneous cancer patients. They found a four cluster solution with one group (15% of the sample) that had low fatigue and high pain, one group that had high fatigue and low pain (35% of the sample), one group with low levels of all symptoms including depression and sleep disturbance (35% of the sample), and one group (28% of the sample) with higher levels of all symptoms than the other three groups. Participants in the "all low" group had higher physical functional status and better quality of life than participants in the three other groups. The authors also found that the sample could be reduced to a two-cluster solution, with one group (85% of the sample) having low to moderate levels of all symptoms, and one group (15% of the sample) with high levels of all symptoms (Miaskowski, et al., 2006).

Pud and colleagues (2008) conducted a cross-sectional study of 228 heterogeneous oncology outpatients under active treatment in Israel. They measured fatigue, pain, depression, and sleep disturbance. Similar to Miaskowski and colleagues, they found that the sample could be divided into four groups: one group with moderate fatigue and high pain (42% of the sample), one group with high fatigue and low pain (18% of the sample), an "all low" group (33% of the sample), and an "all high" group (7% of the sample). Like Miaskowski and colleagues, Pud and colleagues found that the four groups could be collapsed into a two-cluster solution, with one group reporting mostly low-to-moderate levels of all symptoms (93% of the sample) and one group reporting high levels of all symptoms (7% of the sample) (Pud, et al., 2008).

Dodd and colleagues (2010) studied 112 breast cancer patients over time, from the week before the second cycle of chemotherapy until one year after starting chemotherapy, and used cluster analysis at each point in time to form groups based on scores in four symptoms: fatigue, pain, depression, and insomnia. They identified four groups: "all low" (one or fewer symptoms above the cut-point),"mild" (patients who scored beyond the cut-point of two symptoms), "moderate" (patients who scored beyond the cut-point of three or four symptoms), and "all high" (patients with all four symptoms above the cut-point). The authors found that by the final follow-up, there was no longer an "all low" group. They also noted that the group with the lowest level of symptom burden had significantly better quality of life and physical function compared to the groups with greater symptom burden. They also noted that employment status was the only demographic variable that differed between the group; women in the "all low" group were employed (Dodd, et al., 2010).

Rationale for study

Despite recent advances in the study of symptom clusters, symptom clusters remain poorly understood (Miaskowski & Aouizerat, 2007; Xiao, 2010) particularly in relation to functional outcomes. Although past research has explored the relationship between individual symptoms among those diagnosed with cancer, such as fatigue or depression, and work measures, such as work hours or work ability, there is no known research that relates symptom clusters to work outcomes in cancer survivors. Further, the literature on symptom clusters has generally focused on cancer patients who may still be in treatment rather than cancer survivors following primary treatment (Fan, et al., 2007). It is unknown whether symptom clusters are present in cancer survivors several years after completion of treatment. Therefore it is unknown whether symptom clusters are related to work outcomes in working cancer survivors. To the author's knowledge, this is the first study to examine symptom clusters in a sample of working cancer survivors. This is also the first study to relate symptom clusters to a work-related outcome.

Aims & hypotheses

The first aim of the study was to determine whether employed breast cancer survivors, as well as a non-cancer comparison group, can be classified based on distinct patterns of symptom burden. It was expected that participants in each population could be grouped based on distinct symptom patterns.

The second aim of the study was to determine whether the observed patterns of symptoms in breast cancer survivors and a non-cancer comparison group are related to differences in work limitations. Given the evidence on the relationship between individual symptoms and work ability in cancer survivors, it was expected that greater degree of symptom burden (i.e. fatigue, cognitive limitations, depressive symptoms, anxiety symptoms, and pain) would be associated with a higher level of work limitations experienced by cancer survivors and the comparison group.

METHODS

Data collection

This study used previously collected data from two studies of working breast cancer survivors (Calvio, et al., 2010; Hansen, et al., 2008). Both studies were conducted using online surveys, and all data was collected using self-report. The two studies recruited participants by posting notices in newspaper advertisements, cancer websites, hospital support groups, and at cancer survivor events. Both studies recruited employed breast cancer survivors as well as an employed comparison group of women without a history of cancer. Participants of Study 1 included 100 breast cancer survivors and 103 women in the non-cancer comparison group. Participants of Study 2 included 149 breast cancer survivors and 132 women in the non-cancer comparison group.

Inclusion criteria for Study 1 were female gender, age 20-70, working for at least one year before the study, and internet access. Cancer survivors were included if they had been diagnosed with breast cancer Stages I-III and had completed primary treatment. Participants in the comparison group were included if they had no history of cancer. Inclusion criteria for Study 2 were female gender, age 18-65, working for at least one year before the study, and internet access with speed higher than dial-up. Cancer survivors were included if they had been diagnosed with breast cancer Stages I-III and between 1-10 years had elapsed since completion of primary treatment. Participants in the comparison group were included if they had no history of cancer. Exclusion criteria were history of dementia, brain injury, adult Attention Deficit Hyperactivity Disorder, epilepsy, and drug or alcohol abuse.

Measures

Participants reported demographic information (marital status, age, education level and race) and job information (job type and level of job stress). Breast cancer survivors reported medical variables including tumor location, tumor stage, type of treatment received, and time since diagnosis (Study 1) or time since completion of primary treatment (Study 2).

Both samples used the same self-report measures to assess anxiety symptoms, depressive symptoms, fatigue, cognitive limitations, and work limitations. Although pain has been a component of previous symptom cluster research, it could not be included in the present study because it was not measured in both of the prior studies. In order to assess the reliability of the clusters by repeating the same analysis on two separate samples, this study only examined symptoms that were measured using the same instruments in both of those prior studies.

Hospital Anxiety and Depression Scale (HADS): The HADS was developed to assess symptoms of anxiety and depression in a population of persons with a medical condition (Zigmond & Snaith, 1983). It emphasizes affective symptoms rather than somatic symptoms in order to avoid confounding of symptoms commonly experienced by medical patients. The HADS has been validated repeatedly in populations of patients with psychiatric as well as medical conditions, including cancer (Annunziata, Muzzatti, & Altoe, 2010; Bjelland, Dahl, Haug, & Neckelman, 2002; Moorey, et al., 1991). The HADS has 14 items and uses a 4-point Likert scale. It has two subscales: a 7-item A scale assesses anxiety symptoms, and a 7-item D scale assesses depressive symptoms. This study used the A scale and D scale separately to report symptoms of anxiety and depression.

Multidimensional Fatigue Symptom Inventory, Short Form (MFSI-SF): The MFSI-SF is an abbreviated version of a measure that was developed to assess fatigue in cancer patients (Stein, Jacobsen, Blanchard, & Thors, 2004; Stein, Martin, Hann, & Jacobsen, 1998). The MFSI-SF comprises 30 items using a 5-point Likert scale. It contains subscales for four distinct aspects of fatigue: physical fatigue, emotional fatigue, mental fatigue, and vigor. The MFSI-SF has been validated on breast cancer patients as well as a comparison group of women without a history of cancer (Stein, et al., 1998) and a sample of patients with different types of cancer (Stein, et al., 2004). This study only used the 5-item physical fatigue subscale in order to minimize overlap with other symptom measures.

Cognitive Symptom Checklist, modified (CSC): The CSC-modified measures cognitive limitations that affect a person at work (Feuerstein, et al., 2007; O'Hara, Harrell, Bellingrath, & Lisicia, 1993). The original measure was shortened to 59 items by Feuerstein and colleagues, who performed a factor analysis that identified three distinct subscales: executive function, memory, and attention (Feuerstein, et al., 2007). This study used the total CSC-modified score to measure cognitive limitations at work.

Work Limitations Questionnaire (WLQ): The WLQ was developed to assess the "on the job" impact of various chronic illnesses (Lerner, et al., 2001). It was validated on a heterogeneous population of persons with chronic illnesses (e.g. asthma, Chron's disease, depression, anxiety, epilepsy) and a job-matched control group (Lerner, et al., 2001). The full measure comprises 25 items using a 5-point Likert scale. This study used the 5-item work output subscale, which asks respondents to report how much of the time their physical health or emotional problems made it difficult to manage their workload and accomplish various work tasks. The WLQ has been validated against objective measures of workplace productivity (Lerner, et al., 2003).

Analyses

All analyses were performed using SPSS 16 statistical software. Study 1 had 100 breast cancer survivors and 103 participants in the comparison group. Participants who were missing more than 20% of items on any symptom measure or the work outcome measure were excluded. Under this criteria, nine cases were excluded: six cases from the breast cancer survivor group and three cases from the comparison group, yielding new totals of 94 breast cancer survivors and 100 comparison cases. Study 2 had 149 breast cancer survivors and 132 participants in the comparison group. Using the same criteria to exclude cases with missing data, 26 cases were excluded from Study 2: 15 cases were excluded from the breast cancer survivor group and 10 were excluded from the comparison group, yielding new totals of 134 breast cancer survivors and 122 comparison cases. Breast cancer survivors and the comparison group in each dataset were compared on demographic and medical variables using t-tests for continuous variables and chi-squared tests for categorical variables.

For cases missing 20% or fewer items per measure, scores were imputed by calculating each participant's mean response on all items in a measure, multiplied by the number of items in the measure. In Study 1, two participants had the HADS A score imputed; four participants had the HADS D score imputed; two participants had the MFSI score imputed; and 52 had the CSC score imputed. (Because the CSC consists of 59 items and the other measures each consist of between 5-7 items, a far greater number of participants were missing at least one item on the CSC compared to the other measures). Following the imputations, new descriptive statistics were calculated for symptom measures in each sample, and standardized scores were calculated for all participants in each sample. Symptom measure scores were converted to standardized scores in order to prevent any individual symptom from contributing disproportionately to the formation of clusters.

Participants were grouped using hierarchical agglomerative cluster analysis (Clatworthy, Buick, Hankins, Weinman, & Horne, 2005). The similarity measure was squared Euclidean distance and cluster method was Ward's method (Clatworthy, et al., 2005). The four symptom measures (anxiety symptoms, depressive symptoms, fatigue, and cognitive limitations) were the variables entered to form the clusters.

Because cluster analysis is an exploratory technique that can be unreliable, internal reliability was calculated using the nearest-centroid technique described by McIntyre and Blashfield (McIntyre & Blashfield, 1980). In addition, the current study determined the reliability of its results by repeating the cluster analysis on separate datasets, Study 1 and Study 2. To examine the formation of clusters in breast cancer survivors as well as a comparison group, the analysis was also run separately on those two groups within each dataset. Therefore a separate cluster analysis was run on each of the four samples: Breast Cancer Survivors, Study 1; Comparison Group, Study 1; Breast Cancer Survivors, Study 2; Comparison Group, Study 2. Because cluster analysis was performed separately on each of the four populations, standardized scores were calculated separately for each population as well.

Clusters were identified by visually examining the dendrogram and examining the output of the agglomeration schedule. This method used the relative distance scale to determine a cluster solution (i.e. optimal number of clusters within the sample) that would maximize similarity within clusters and minimize similarity between clusters. After determining the optimal cluster solution, that target number of clusters was entered into SPSS, which generated cluster assignments for all participants. In order to confirm that clusters differed on the input variables (anxiety symptoms, depressive symptoms, fatigue, and cognitive limitations), univariate analyses of variance were performed with cluster assignment as the independent variable and the four symptom measures as the dependent variables.

Each of the four sets of clusters were then compared on demographic and medical variables using t-tests and chi-squared tests. Any demographic or medical variable in which clusters were at least marginally significantly different ($p < .1$) was considered a potential confounder. The different clusters within each sample were then compared using a one-way analsis of variance with cluster assignment as the independent variable and work limitations as the dependent variable, with potential confounders entered as co-variates.

RESULTS

Descriptive statistics

Study 1 had 94 participants with history of breast cancer and 100 participants in the comparison group. Study 2 had 134 participants with history of breast cancer and 122 in the comparison group. Demographic information for the four study populations appears in Table 1, and medical information for breast cancer survivors appears in Table 2. Symptom scores and work limitations scores for the four study populations appear in Table 3.

Table 1: Demographic characteristics

	Study 1		Study 2	
Characteristic	Breast cancer (n = 94)	Comparison (n = 100)	Breast cancer (n = 134)	Comparison (n = 122)
Age[1,2]	49.45 (8.45)	39.90 (10.81)	44.88 (9.14)	39.10 (11.96)
Education				
Some college or less	27.7%	17.0%	22.4%	22.1%
Associates or bachelors	31.9%	20.0%	31.3%	35.3%
Graduate	40.4%	63.0%	46.3%	42.6%
Relationship status[3,4]				
Single, divorced, separated, or widowed	34.0%	42.0%	24.1%	45.5%
Married or cohabitating	66.0%	58.0%	75.9%	54.5%
Race				
White	91.5%	89.0%	86.6%	65.6%
Non-white	8.5%	11.0%	13.4%	34.4%
Job type[5]				
Managerial	26.6%	24.0%	35.9%	33.6%
Professional	45.7%	62.0%	44.3%	47.5%
Sales, service, clerical	27.7%	14.0%	19.8%	18.9%

[1] In Study 2 breast cancer group, 12 respondents are missing (n = 122).
[2] In Study 2 comparison group, 9 respondents are missing (n = 113).
[3] In Study 2 breast cancer group, one respondent is missing (n = 133).
[4] In Study 2 comparison group, one respondent is missing (n = 121).
[5] In Study 2 breast cancer group, three respondents are missing (n = 131).

Table 2: Medical characteristics of participants with history of breast cancer

	Study 1 (n = 94)	Study 2 (n = 134)
Tumor location[1,2]		
Right	41.9%	51.9%
Left	53.8%	44.4%
Both	4.3%	3.8%
Tumor stage at diagnosis[1,3]		
I	41.9%	36.4%
II	41.9%	47.0%
III	16.1%	16.7%

Treatment type		
Chemotherapy	77.7%	82.8%
Radiation	67.0%	73.9%
Surgery	92.6%	97.0%
Tamoxifen/ Raloxifene[4]	--	44.0%
Herceptin[4]	--	13.4%
Other	33.0%	23.9%
Time in years[5,6,7]	3.49 (3.57)	3.08 (2.38)

[1]In Study 1, one respondent is missing (n = 93)
[2] In Study 2, one respondent is missing (n = 133).
[3] In Study 2, two respondents are missing (n = 132).
[4] Study 1 did not ask about Tamoxifen, Raloxifene, or Herceptin.
[5] Study 1 asked participants to report time since diagnosis. Study 2 asked participants to report time since completion of primary treatment.
[6] In Study 1, two respondents are missing (n = 92).
[7] In Study 2, four respondents are missing (n = 130).

Table 3: ***Symptom measures and work limitations for each sample***

	Study 1				Study 2			
	Breast Cancer		Comparison		Breast Cancer		Comparison	
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
HADS A (Anxiety)	7.48	4.66	5.97	3.37	7.70	3.03	7.10	2.68
HADS D (Depression)	4.57	3.58	3.08	2.70	4.53	3.33	3.27	2.76
MFSI (Fatigue)	4.90	4.16	2.08	2.61	5.44	4.76	2.18	2.47
CSC (Cognitive Limitations)	18.97	12.97	11.58	9.64	17.29	12.76	8.20	6.97
WLQ (Work Limitations)	3.69	4.02	1.80	2.50	3.61	3.95	1.61	2.43

Cluster formation

Hierarchical cluster analysis was performed separately on each of the four samples (Breast Cancer Survivors, Study 1; Comparison Group, Study 1; Breast Cancer Survivors, Study 2; Comparison Group, Study 2). Examination of the dendrograms and agglomeration schedules for the four samples revealed a two-cluster solution in each sample. Kappa statistics for internal reliability are as follows: Breast Cancer Survivors, Study 1: .892; Breast Cancer Survivors, Study 2: .594; Comparison Group, Study 2: .848. Symptom scores for the two clusters in each population are displayed in Figures 1 and 2 and are listed in Table 4. Univariate analysis of variance was performed in each of the four samples to confirm that in each sample, the two clusters differed on each symptom. The results of each ANOVA are listed in Table 4. In each sample, one cluster of participants ("high" group) had higher scores of anxiety symptoms, depression symptoms, fatigue, and cognitive limitations, and one cluster ("low" group) had lower scores on the four symptom measures. In the breast cancer survivor sample in Study 1, 63 participants were in the high group and 31 were in the low group. In the comparison group sample in Study 1, 24 participants were in the high group and 76 were in the low group. In the breast cancer survivor sample in Study 2, 64 participants were in the high group and 70 were in the low group. In the comparison group sample in Study 2, 77 participants were in the high group and 44 were in the low group.

Table 4: Symptom measures for the two clusters in each sample

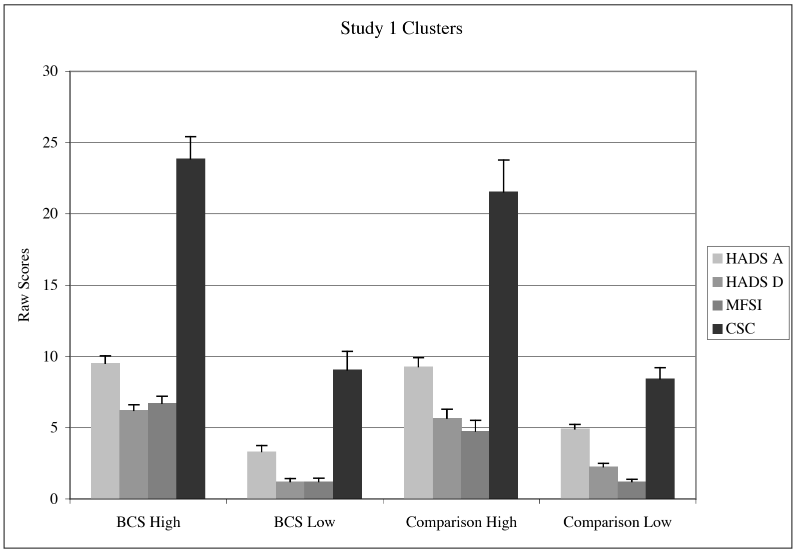
	Study 1									
	Breast Cancer					Comparison				
	"High Group" (n = 63)		"Low Group" (n = 31)		F	"High Group" (n = 24)		"Low Group" (n = 76)		F
Measure	*M*	*SD*	*M*	*SD*		*M*	*SD*	*M*	*SD*	
HADS A***	9.52	4.15	3.33	2.27	59.86	9.29	3.04	4.92	2.74	44.17
HADS D***	6.21	3.21	1.23	1.15	70.28	5.67	3.09	2.26	1.96	40.70
MFSI***	6.71	3.88	1.23	1.31	58.50	4.77	3.69	1.22	1.33	50.30
CSC***	23.85	12.41	9.06	7.16	37.70	21.55	10.87	8.43	6.67	50.74

***p<.001

	Study 2									
	Breast Cancer					Comparison				
	"High Group" (n = 64)		"Low Group" (n = 70)		F	"High" (n = 77)		"Low Group" (n = 45)		F
Measure	*M*	*SD*	*M*	*SD*		*M*	*SD*	*M*	*SD*	
HADS A***	9.37	2.81	6.18	2.35	51.16	8.01	2.68	5.54	1.83	30.16
HADS D***	6.68	3.11	2.56	2.08	82.48	4.34	2.79	1.42	1.39	43.06
MFSI***	9.22	4.08	1.99	1.76	183.25	3.14	2.62	0.53	0.73	42.46
CSC***	25.05	12.44	10.20	8.08	68.29	11.46	6.74	2.63	2.22	72.47

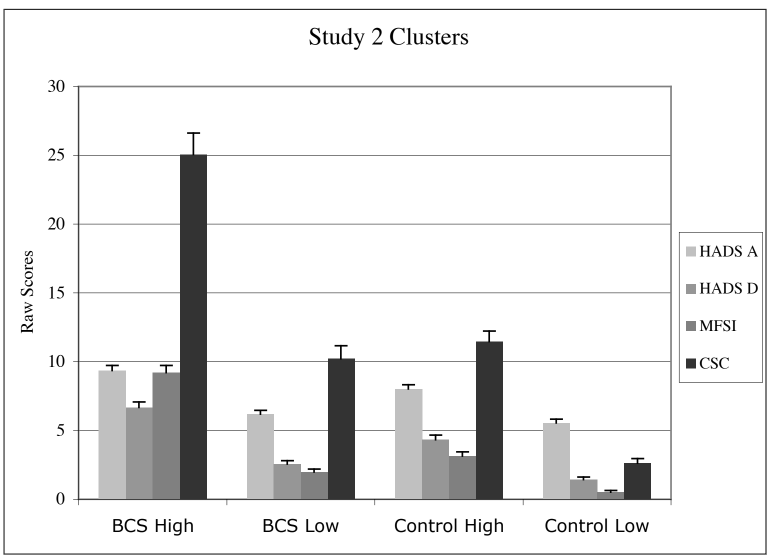
***p<.001

Figure 1: Raw symptom scores of high and low groups, Study 1



Note: Error bars indicate 1 standard error.

Figure 2: Raw symptom scores of high and low groups, Study 2



Note: Error bars indicate 1 standard error.

Demographic and medical differences between high and low symptom groups

In each of the four samples, the high and low groups were compared on demographic and medical variables. In Study 1, the breast cancer survivor high and low groups did not significantly differ on any demographic variables. The high and low groups did not differ on any medical variables except for years since diagnosis: The participants in the high symptom group reported that fewer years had passed since diagnosis (M = 2.85, SD = 2.93) than the participants in the low group (M = 4.74, SD = 4.37), $t(90) = -2.173$, p = .035. The high and low groups of the comparison sample in Study 1 did not differ on any demographic variables. The high and low symptom groups in the Study 1 comparison sample did not differ on any demographic variables.

In Study 2, the breast cancer survivor high and low groups significantly differed on multiple demographic variables. A chi-square test determined that education level differed between the high and low groups, X^2 (2, N = 134) = 9.192, p = .010. In the high group, 32.8% of participants had completed at least some graduate school, compared to 58.6% of participants in the low group. The high and low groups also differed on race, X^2 (1, N = 134) = 5.436, p = .020. In the high group, 93.8% of participants were white, compared to 80.0% in the low group. The high and low groups also differed with respect to job type, X^2 (2, N = 131) = 6.776, p = .034. The high and low groups in the breast cancer survivor sample only differed on one medical variable, tumor stage, X^2 (2, N = 132) = 6.288, p = .043. In the high group, 73.5% of participants reported having stage II or III cancer at diagnosis, compared with 52.9% of participants in the low group. The high and low groups in the Study 2 comparison sample did not differ on any demographic variables.

Differences in work limitations between high and low symptom groups

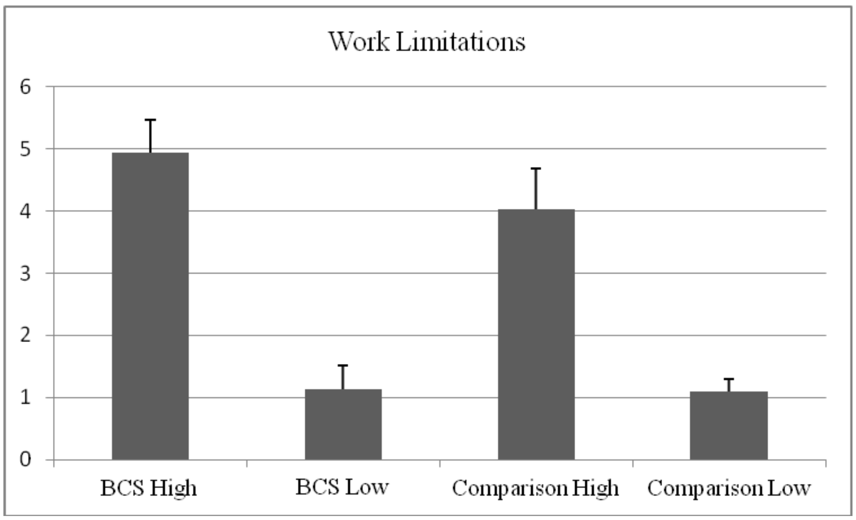
In each of the four samples (Breast Cancer Survivors, Study 1; Comparison Group, Study 1; Breast Cancer Survivors, Study 2; Comparison Group, Study 2), the high and low symptom groups were compared with group assignment as the independent variable and work limitations as the dependent variable. Demographic and medical variables on which the high and low symptom groups were at least marginally significantly different were entered as covariates. There were no covariates in the comparison groups in Study 1 or Study 2. However in the breast cancer survivor sample of Study 1, years since diagnosis was entered as a covariate. In the breast cancer survivor sample of Study 2, education, race, job type, and breast cancer stage were entered as covariates.

An analysis of covariance showed that group assignment was significant in each of the four samples. The participants in the high symptom group reported significantly greater work limitations than the low symptom group in each of the four samples: Breast Cancer Survivors, Study 1, $F(1,92) = 22.991$, $p < .001$; Comparison Group, Study 1, $F(1,98) = 33.528$, $p < .001$; Breast Cancer Survivors, Study 2, $F(1,116) = 40.700$, $p < .001$; and Comparison Group, Study 2, $F(1,116) = 7.587$, $p = .007$. High/low group assignment significantly accounted for work limitations even after controlling for confounding variables. The mean work limitations score for each of the groups is listed in Table 5 and displayed Figures 3 and 4.

Table 5: Work lmitations output scale, high and low symptom groups

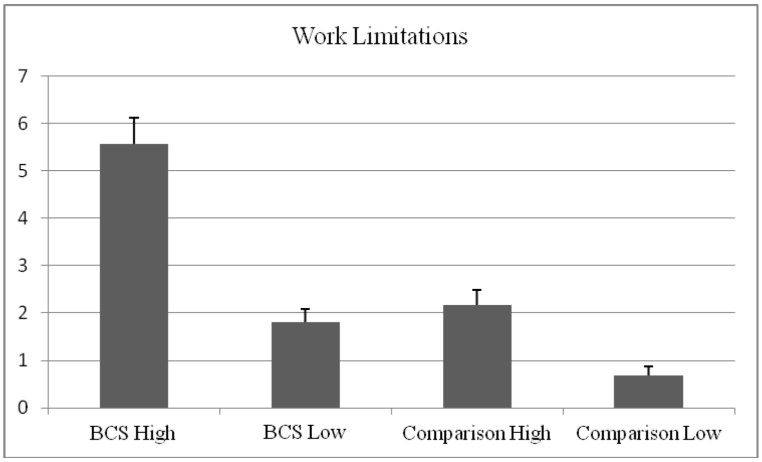
	Study 1				Study 2			
	Breast Cancer		Comparison		Breast Cancer		Comparison	
	“High Group” (n = 63)	"Low Group" (n = 31)	“High Group” (n = 24)	"Low Group" (n = 76)	“High Group” (n = 64)	"Low Group" (n = 70)	“High Group” (n = 77)	"Low Group" (n = 45)
WLQ	4.94 (4.18)	1.14 (2.03)	4.03 (3.22)	1.10 (1.71)	5.57 (4.40)	1.81 (2.35)	2.16 (2.77)	0.69 (1.29)

Figure 3: Work limitations output scale, Study 1



Note: Error bars indicate 1 standard error.

Figure 4: Work limitations output scale, Study 2



Note: Error bars indicate 1 standard error.

DISCUSSION

Summary of results

Four samples—two samples of working breast cancer survivors and two samples of a working non-cancer comparison group—were grouped into high and low symptom groups using cluster analysis based on reports of anxiety, depressive symptoms, fatigue, and cognitive limitations. In each sample, one group reported higher mean levels of all four symptoms compared with the other group. In addition, in each of the four samples, the high symptom group reported more limitations in work outcomes compared to the low symptom group. These results remained consistent when analyses were repeated across all four samples, and the difference in work limitations between high and low symptom groups appeared even after controlling for potential confounders in each sample. This study provides new knowledge regarding the relationship between a set of symptoms experienced several years post-diagnosis by survivors and work output.

Comparison with past research

Research on symptom clusters is still in its infancy. Most prior studies symptom clusters in cancer have used cluster analysis or factor analysis to identify clusters of symptoms that co-occur, but a few prior studies have used cluster analysis to identify groups of patients with similar patterns of symptoms (Dodd, et al., 2010; Miaskowski, et al., 2006; Trask & Griffith, 2004). Like those prior studies, this study found that people with a history of breast cancer could be grouped into "low" and "high" symptom groups. Unlike those other studies, this study did not find more types of subgroups (e.g. high fatigue/low pain). This difference could be due to the fact that this study did not examine some of the symptoms assessed in the other studies, e.g. pain and sleep disturbance. The difference could also be due to the sample (cancer survivors several years post-treatment vs. cancer patients; an entirely working sample vs. a combination of working and non-working individuals with cancer), or due to differences in statistical clustering technique.

Because most of the literature on symptom clusters in cancer has been published in the last decade, many questions regarding symptom cluster research are still unresolved. Molassiotis and colleagues (Molassiotis, et al., 2010) identified several of those unresolved questions, including the following: What is the minimum number of symptoms necessary to form a cluster? What is the most appropriate statistical method for determining the presence of symptom clusters? What scales should be used to measure symptoms, and what are the appropriate cut-off points for symptom severity? How should presence, frequency, and/or distress level caused by symptoms be considered in the formation of clusters? How, if at all, should symptom clusters be measured over time for stability? Is it preferable to study symptom clusters on populations that are more homogeneous or more heterogeneous with regard to disease characteristics? The present study was designed to explore the presence of symptom clusters in working breast cancer survivors, who were an average of 3-3.5 post-diagnosis or treatment, respectively, while recognizing that these methodological questions about symptom clusters in cancer remain open for discussion in the field.

The elevation of all four symptoms in a subset of participants supports the concept of a shared biological mechanism, which may account for shared variation in these symptoms (Cleeland, et al., 2003). Alternatively, it is possible that symptoms are elevated together because of interaction among them; for example, greater levels of fatigue may impair a person's function, leading the person to become discouraged and depressed. In this manner, changes in one symptom may have a spread effect on a number of other symptoms.

Strengths and limitations

By using cluster analysis to group working breast cancer survivors based on patterns of four symptoms, this study provided a novel perspective on symptom burden in cancer survivors. To the author's knowledge, this was the first study to examine clusters of symptoms in cancer survivors, rather than cancer patients. In addition, this was the first study to relate symptom clusters to the level of work limitations experienced by cancer survivors. Additional strengths of this study include the replication of its findings, which supports the reliability of the existence of "high"/"low" groups that are related to lower work output.

This study has some limitations. The present study did not conduct any formal testing to assess whether a two-cluster solution is more robust than another solution (e.g. three or four clusters). This will be explored in further analyses.

Given the study's cross-sectional design, it is impossible to determine any causality between symptom burden and work limitations. The cross-sectional design also does not reveal the possible time-course of symptom clusters. The finding in Study 1 that the high symptom group of breast cancer survivors had been diagnosed more recently than the low symptom group raises the question of whether these symptoms decline together over time, and how if at all group assignment would change as more time elapsed since diagnosis and completion of treatment. Therefore, future research should use a prospective longitudinal design to assess the stability of high/low symptom groups over time. This longitudinal perspective has been used in some prior studies (Dodd, et al., 2010), who found that by the final follow-up, the "all low" group had disappeared, and all survivors were distributed in the moderate or higher symptom groups.

Because all symptoms were measured by self-report, the data collected was subjective and varied in some part based on the response styles of the individual participants. Some participants may have simply been more likely to endorse symptoms across multiple self-report measures, regardless of differences in objective symptom level. Therefore the results are subject to response bias. Alternatively, a greater tendency to report symptoms (whether or not such symptom reporting correlates with objective symptom measures) could itself indicate a shared psychological mechanism that places a person at risk for adverse work outcomes. Future studies could address the question of response bias by performing additional types of measurement, such as observer ratings from collateral informants (e.g. significant others, colleagues) or formal assessments. Further research could also administer measures of response bias and symptom-reporting tendencies in order to address these potential confounds.

The study is further constrained by its examination of only four symptoms. Other symptoms such as pain and sleep disturbance have been studied as part of symptom clusters in cancer patients (Dodd, et al., 2010; Miaskowski, et al., 2006; Trask & Griffith, 2004). These symptoms are known to cluster together with depression, fatigue, and cognitive limitations (Bender, et al., 2005; H. Kim, et al., 2008; Thornton, et al., 2010), and may also be important in accounting for the relationship between symptom burden and work limitations.

Implications

The findings of this study suggest that it may be useful for occupational health providers to assess patterns of multiple symptoms in employed cancer survivors who report work limitations. Looking at the overall pattern of multiple symptoms is particularly useful when individual symptoms are elevated but do not reach clinical thresholds. By recognizing distinct patterns of symptoms that are related to adverse work outcomes, practitioners may be better positioned to provide targeted, coordinated care that can improve multiple symptoms and concomitantly work output. Attending to symptom clusters rather than individual symptoms may improve the integration of care by widening clinical focus to encompass patterns of symptoms and underlying mechanisms as well as by identifying specific patterns that require intervention rather than individual complaints. This shift in focus could improve the understanding of how symptoms are experienced as well as how they can be managed. These assumptions require further empirical verification, but can serve as promising potential approaches to the management of symptom burden.

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